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Impaired Immune Health in Survivors of Diffuse Large B-Cell Lymphoma

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abstract

PURPOSE Therapeutic advances for diffuse large B-cell lymphoma (DLBCL) have led to an increasing number of survivors. Both DLBCL and its treatments perturb the immune system, yet little is known about immune health during extended survivorship.

METHODS In this retrospective cohort study, we compared 21,690 survivors of DLBCL from the California Cancer Registry (CCR) to survivors of breast, prostate, head and neck, and melanoma cancers. We linked their CCR records to a statewide database documenting hospital, emergency room, and ambulatory surgery visits and investigated the incidence of autoimmune conditions, immune deficiencies, and infections 1-10 years after cancer diagnosis.

RESULTS We found elevated incidence rate ratios (IRRs) for many immune-related conditions in survivors of DLBCL compared with other cancer survivors, including significantly and consistently elevated IRRs for viral and fungal pneumonias (up to 10.8-fold), meningitis (up to 5.3-fold), as well as humoral deficiency (up to 17.6-fold) and autoimmune cytopenias (up to 12-fold). IRRs for most conditions remained high even in the late survivorship period (5-10 years after cancer diagnosis). The elevated risks could not be explained by exposure to chemotherapy, stem-cell transplantation, or rituximab, except for IRRs for humoral deficiency, which were consistently higher after the incorporation of rituximab into DLBCL treatments.

CONCLUSION To our knowledge, this is the largest cohort study with extended follow-up to demonstrate impaired immune health in survivors of DLBCL. The observed persistent, elevated risks for autoimmune diseases, immune deficiencies, and infectious conditions may reflect persistent immune dysregulation caused by lymphoma or treatment and may lead to excess morbidity and mortality during survivorship. Improved understanding of these risks could meaningfully improve long-term care of patients with DLBCL.

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ASSOCIATED CONTENT

See accompanying Editorial on page 1648

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), the most common B-cell non-Hodgkin lymphoma, is an aggressive lymphoma that is fatal without treatment but curable with current therapies. Survival for patients with DLBCL has improved significantly since rituximab, a monoclonal antibody against the B-cell protein CD20, was introduced in 1997, soon becoming the standard of care.[1-5] Treatment with rituximab plus combination chemotherapy and corticosteroids results in 50%-75% 5-year survival[3,6] and has resulted in an increasing number of long-term survivors. Although it has been demonstrated that survivors of DLBCL suffer from cardiac disease,[7-9] neuropathy,[7,10,11] secondary malignancies,[12,13] decreased bone density,[14] and other conditions,[7,8,15-17] little is known about their immune health.

As a cancer of immune cells, DLBCL perturbs immune networks, resulting in qualitative and quantitative dysfunction via a reduction in normal B cells and loss of normal communication between B cells and other immune cells.[18-20] In addition, treatments for DLBCL, including rituximab,[21,22] corticosteroids,[23] newer agents such as lenalidomide,[24] and radiotherapy and chemotherapy,[25] all have profound effects on the immune system. Whether these result in lasting changes to immune function, especially changes that might persist in the absence of active disease and treatment, is unknown.

Certain autoimmune diseases, immune deficiency syndromes, and infections are associated with the pathogenesis of DLBCL, but the majority of DLBCL cases arise in the absence of such conditions.[26-32] To our knowledge, no studies have assessed whether survivors of DLBCL have altered risk of developing new-onset autoimmune and infectious diseases or immune deficiencies during mid- to long-term survivorship due to disease- or treatment-related immune impairments.

Knowledge of such risks could lead to improved care of survivors of lymphoma and to new strategies for mitigating these risks.

Therefore, we created a large retrospective cohort using population-based California Cancer Registry (CCR) data, which we linked to individual-level data on hospitalizations and emergency department and ambulatory surgery visits from the California Office of Statewide Health Planning and Development (OSHPD). In this cohort of DLBCL survivors, we examined the incidence of autoimmune diseases, immune deficiencies, and infectious diseases and compared them to incidence in similarly constructed cohorts of breast cancer, prostate cancer, head and neck cancer, and melanoma survivors. To focus on conditions with onset during survivorship, we excluded diagnoses identified before or within 1 year after cancer diagnosis. We chose comparison cohorts to include cancers with high disease-free, treatment-free survival rates (breast, prostate, melanoma), use of high-intensity initial therapy (head and neck cancer), and nonepithelial origin (melanoma).

METHODS

Data Source and Population

Eligible persons in the CCR database were age ≥ 18 years, resided in California when diagnosed with one of 5 primary invasive cancers (DLBCL, breast cancer, prostate cancer, head and neck cancer, and melanoma) between January 1, 1991 and December 31, 2012, and survived ≥ 1 year from diagnosis; HIV/AIDS was exclusionary (Data Supplement). Patient records were linked to OSHPD discharge records from hospitalizations, emergency room visits, and ambulatory surgery encounters. Please see the Data Supplement for details of derivation of cohorts and subcohorts used for sensitivity analyses.

All study protocols were overseen by the institutional review board of the University of California, Davis and by the California Committee for the Protection of Human Subjects.

Identification and Classification of Immune-Related Conditions

Informed by prior studies,[28,33] we identified 595 International Classification of Diseases 9th revision (ICD-9) codes for conditions we considered immune related. To avoid comparing diagnoses with very few events in the dataset, our primary analyses used 41 diagnoses that were present at a rate of at least 5 events per 10,000 patients in the DLBCL cohort and two additional diagnoses of clinical interest, dermatomyositis/polymyositis and autoimmune hepatitis (Data Supplement). A secondary analysis included all 595 immune-related ICD-9 codes grouped into 18 diagnostic categories (Data Supplement).

Statistical Analyses

We used descriptive statistics to characterize each cohort. We compared the incidence of autoimmune and infectious diseases and immune deficiencies among survivors of DLBCL with each of the other survivor cohorts during the 1-10–year period after cancer diagnosis. We estimated incident rate ratios (IRRs) using multivariable Poisson regression models adjusted for age at cancer diagnosis (18-39, 40-64, and ≥ 65 years), sex, race/ethnicity (white, Hispanic, and other), and year of cancer diagnosis (1991-1996, 1997-2002, 2003-2007, and 2008-2012). We used negative binomial models when overdispersion was evident. For the comparisons to survivors of female breast cancer and survivors of prostate cancer, we included only female and only male survivors of DLBCL, respectively. To focus on diseases with onset during survivorship, we excluded conditions occurring before or within 1 year after cancer diagnosis. To account for multiple comparisons, we applied a *P*-value threshold of ≤ .0002 for interpretation of statistical significance on the basis of a Bonferroni correction[34] with 43 primary and 18 secondary diagnoses in 4 pairwise comparisons.

To evaluate risks over time, we estimated the cumulative incidence of a subset of immune-related conditions accounting for death as a competing risk. To quantify the risks in the later survivorship period, we calculated adjusted IRRs comparing survivors of DLBCL to the other survivor cohorts for the late survivorship period 5-10 years after cancer diagnosis, excluding diagnoses seen before the 5-year mark.

All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC).

RESULTS

Characteristics of Survivor Cohorts

The final study population included 21,690 survivors of DLBCL and comparator cohorts of 337,591 survivors of female breast cancer, 325,533 survivors of prostate cancer, 44,245 survivors of head and neck cancer, and 73,196 survivors of melanoma (Data Supplement). These cancer cohorts had relatively similar distributions for age, race/ethnicity, year of cancer diagnosis, neighborhood socioeconomic status (SES), and insurance coverage, except the melanoma cohort, in which patients were more likely to be of non-Hispanic white race/ethnicity, of higher neighborhood SES, and privately insured, and the head and neck cancer cohort, which included a higher proportion of males (Table 1). Survivors of DLBCL were more likely to have advanced-stage disease at diagnosis, but lymphoma is staged differently from the other cancers.[35] A similar proportion of survivors across the cohorts had at least one captured OSHPD encounter in the 1-10–year period after cancer diagnosis (range, 73%-78%). The median number of encounters per patient in each cohort was 2.

Survivors of DLBCL Have Increased Risks of Immune-Related Conditions

In comparison with female survivors of breast cancer, female survivors of DLBCL had significantly increased incidence rates for 30 of the 43 conditions included in the

TABLE 1. Characteristics of 1-Year Survivors of DLBCL, Female Breast, Prostate, Melanoma, and Head and Neck Cancers, California, 1991-2012

Characteristic	DLBCL	Female Breast	Prostate	Head and Neck	Melanoma
No. of patients	21,690	337,591	325,533	44,245	73,196
Age, years					
18-39	12	6	0	4	15
40-64	43	55	36	53	49
65-79	34	30	54	34	26
≥ 80	12	9	10	8	10
Sex, % male	53	N/A	N/A	73	55
Race/ethnicity					
Non-Hispanic white	65	69	69	74	89
Non-Hispanic African American	4	6	8	6	0
Hispanic	18	14	13	11	5
Asian/Pacific Islander	12	10	7	8	1
Other/unknown	1	1	3	1	5
Neighborhood socioeconomic status					
Low	51	49	48	55	39
High	48	50	50	43	59
Unknown	2	1	2	1	2
Health insurance					
Private	48	52	44	44	57
Public	37	29	36	34	23
None/unknown	16	19	20	22	21
Stage					
Localized/regional	54	96	91	86	95
Advanced	40	3	4	11	2
Unknown	6	1	5	3	3
Year of cancer diagnosis					
1991-1996	19	24	26	26	19
1997-2002	26	27	27	26	26
2003-2007	26	24	25	23	27
2008-2012	29	25	23	25	28
Follow-up time, years, median (IQR)	6.1 (3.0-10.6)	8.2 (4.5-13.5)	8.3 (4.8-12.8)	5.7 (2.7-10.4)	8.1 (4.4-13.3)
Patients with ≥ 1 encounter within 1-10 years since cancer diagnosis	78.6	75.8	77.7	78.0	72.8
No. of encounters per patient 1-10 years since cancer diagnosis, median (IQR)	2 (1-5)	2 (1-4)	2 (1-5)	2 (1-5)	2 (0-4)

NOTE. Data presented as percentage unless otherwise noted.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; N/A, not applicable.

primary analysis. These included humoral deficiency (IRR, 17.6; 95% CI, 12.4 to 24.9), autoimmune hemolytic anemia (IRR, 12.0; 95% CI, 8.4 to 17.1), fungal pneumonia (IRR, 7.4; 95% CI, 5.1 to 10.9), sicca syndrome (IRR, 4.3; 95% CI, 3.1 to 5.9), viral pneumonia (IRR, 3.9; 95% CI, 2.7 to 5.7), meningitis (IRR, 3.8; 95% CI, 2.2 to 6.5), and systemic lupus erythematosus (IRR, 2.2; 95% CI, 1.5 to 3.1; Fig 1A; Data Supplement). The only diagnosis more frequent in survivors of breast cancer was cervicitis/endocervicitis (IRR, 0.41; 95% CI, 0.27 to 0.61).

Comparing male survivors of DLBCL to survivors prostate cancer, survivors of DLBCL had significantly increased incidence of 28 conditions, including humoral deficiency (IRR, 17.4; 95% CI, 12.6 to 24.1), autoimmune hemolytic anemia (IRR, 11.6; 95% CI, 7.6 to 17.8), fungal pneumonia (IRR, 10.8; 95% CI, 7.7 to 15.2), viral pneumonia (IRR, 6.4;

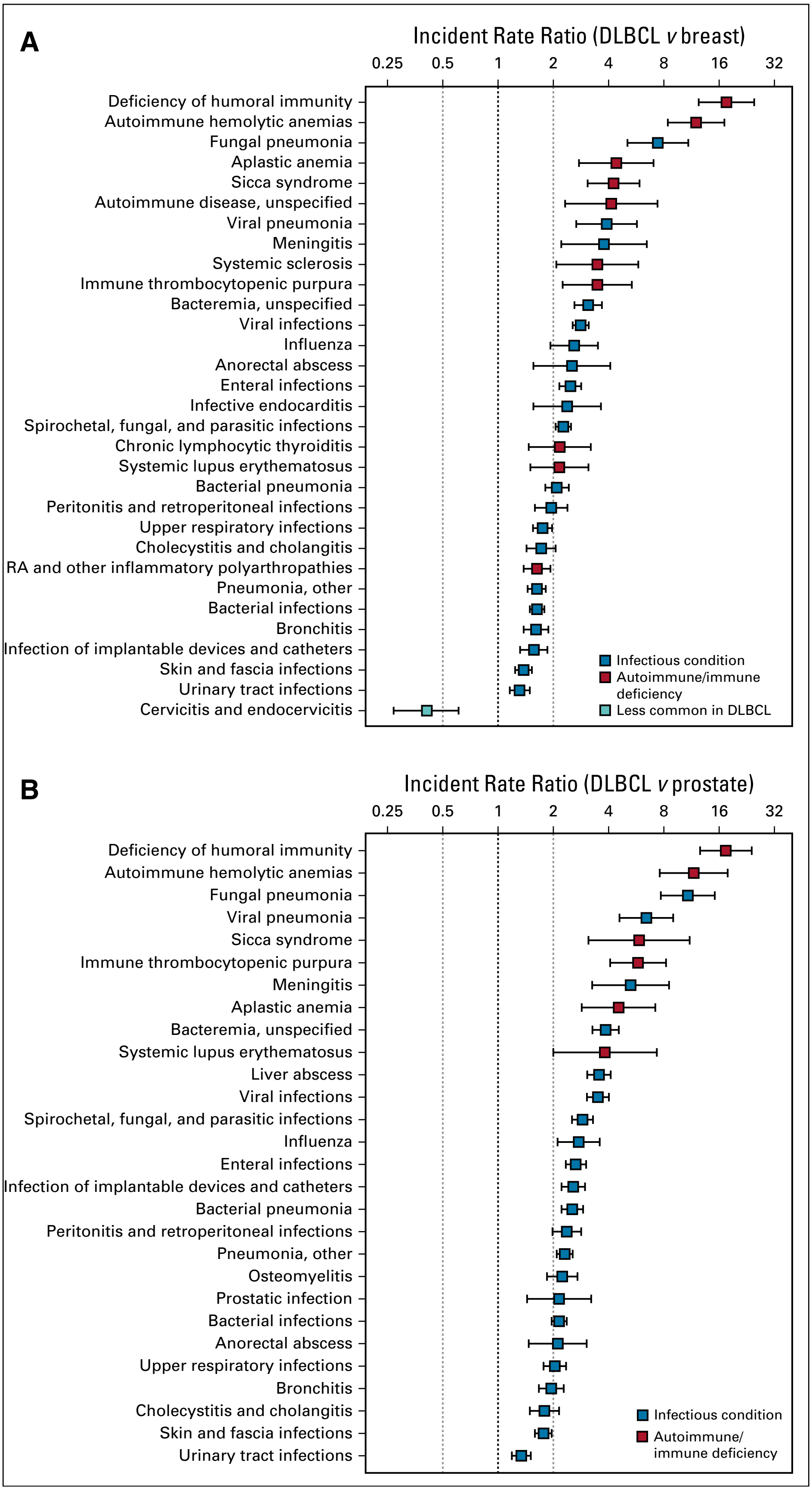

FIG 1. Estimated incidence rate ratios of autoimmune, immune deficiency, and infectious conditions among survivors of B-cell lymphoma (DLBCL) compared with survivors of (A) female breast cancer and (B) prostate cancer in the 1-10 years after cancer diagnosis, California, 1991-2012. Models were adjusted for age, race, and year of cancer diagnosis. Error bars show 95% CIs. Only diagnoses for which the comparison yielded a P value $\leq$ .0002 are shown. Log2 scale is used for the x-axis. RA, rheumatoid arthritis.

95% CI, 4.6 to 9.0), sicca syndrome (IRR, 5.9; 95% CI, 3.1 to 11.1), and meningitis (IRR, 5.3; 95% CI, 3.3 to 8.5; Fig 1B; Data Supplement). No conditions were statistically more frequent among survivors of prostate cancer than male survivors of DLBCL.

When compared with survivors of head and neck cancer, 15 conditions displayed significantly increased incidence rates in survivors of DLBCL, including humoral deficiency (IRR, 11.5; 95% CI, 6.9 to 19.1), autoimmune hemolytic anemia (IRR, 7.7; 95% CI, 4.4 to 13.5), viral and fungal pneumonia (IRR, 4.1; 95% CI, 2.7 to 6.3; and IRR, 3.9; 95% CI, 2.7 to 5.7, respectively), and meningitis (IRR, 3.1; 95% CI, 1.8 to 5.2; Fig 2A; Data Supplement). Notably, survivors of head and neck cancer had an increased incidence of bacterial pneumonias and skin and fascial infections compared with survivors of DLBCL (IRR, 0.49; 95% CI, 0.45 to 0.54; and IRR, 0.77; 95% CI, 0.72 to 0.83, respectively).

Twenty-eight diagnoses were differentially incident when survivors of DLBCL were compared with survivors of melanoma, including humoral deficiency (IRR, 13.2; 95% CI, 9.0 to 19.2), autoimmune hemolytic anemia (IRR, 9.1; 95% CI, 5.8 to 14.3), fungal and viral pneumonias (IRR, 8.5; 95% CI, 5.7 to 12.6; and IRR, 6.6; 95% CI, 4.4 to 9.9, respectively), and sicca syndrome (IRR, 5.3; 95% CI, 3.4 to 8.1; Fig 2B; Data Supplement). No diagnoses were statistically more common in the melanoma cohort.

Excess Risks Are Not Driven by Chemotherapy or Stem-Cell Transplantation and Persist When Patients With Relapsed/Refractory Disease Are Excluded

To control for exposure to systemic therapy, we performed a sensitivity analysis restricting the DLBCL and breast cancer cohorts to patients who received chemotherapy. We found similarly elevated incidence rates in this analysis, including for humoral deficiency (IRR, 20.2; 95% CI, 12.7 to 32.0), autoimmune hemolytic anemia (IRR, 11.3; 95% CI, 7.0 to 18.3), fungal pneumonia (IRR, 7.6; 95% CI, 4.8 to 12.1), viral pneumonia (IRR, 4.6; 95% CI, 3.0 to 7.1), and cervicitis/endocervicitis (IRR, 0.35; 95% CI, 0.22 to 0.54; Data Supplement).

Because stem-cell transplantation (SCT) is used in the treatment of DLBCL but not the other cancer types, we repeated our regression analyses excluding patients in all cohorts who underwent SCT. Consistently across all comparisons, we observed that IRRs were minimally changed relative to the original analysis (Data Supplement). To focus on survivors likely cured by primary therapy, we excluded both patients who underwent SCT and patients who died of their primary cancer. Again, IRRs were largely preserved (Data Supplement).

Rituximab Exposure Relates to Risk for Humoral Deficiency but Not Other Conditions

To evaluate the effects of evolving treatments over time while retaining power to detect low-incidence conditions, we focused on the potential impact of rituximab, the most prominent change in DLBCL treatment during the studied time period. IRRs between survivors of DLBCL and those of other cancers were not consistently different in the pre-rituximab period compared with the post-rituximab period, with the exception of the IRR for humoral deficiency (Data Supplement). This ranged from 5.5-10.9 in the pre-rituximab period, compared with 16.8-20.8 in the post-rituximab period (Data Supplement).

Excess Immune Risks for Survivors of DLBCL Persist Late in Survivorship

To evaluate the relative burden of these excess risks over time, we computed cumulative incidence curves for diagnoses of interest from 1 to 10 years after cancer diagnosis. Cumulative incidence for humoral deficiency, sicca syndrome, autoimmune hemolytic anemia, and immune thrombocytopenia, was considerably higher for survivors of DLBCL than the other cohorts (Fig 3A-3D). Cumulative incidence for many infections, including viral and fungal pneumonias, was also much greater in the DLBCL cohort (Fig 3E-3I). Patients with head and neck cancer accumulated the highest incidence of bacterial pneumonias, followed by survivors of DLBCL (Fig 3J).

To formally quantify risks during late survivorship, when the risk for DLBCL relapse and receipt of salvage therapies is low,[36-38] we estimated IRRs for the period 5-10 years after cancer diagnosis. Here, we still observed significantly elevated IRRs for most conditions, including humoral deficiency (IRRs, 5.7-11.9), autoimmune hemolytic anemia (IRRs, 4.9-9.1), and fungal (IRRs, 4.2-5.7) and viral (IRRs 3.8-4.9) pneumonias (Fig 4). Bacterial pneumonias were seen more commonly in survivors of DLBCL compared with the breast, prostate, and melanoma cohorts (IRRs, 1.6-1.9; $P < .00001$ for all) but less commonly compared with survivors of head and neck cancer (IRR, 0.46; 95% CI, 0.40 to 0.54). The IRRs from this analysis (years 5-10) were only 22% lower on average than those from the primary analysis (years 1-10; Data Supplement). Event counts for the full and the late survivorship periods are presented in Data Supplement.

Survivors of Hodgkin Lymphoma Experience Risks Similar to Survivors of DLBCL

We hypothesized that survivors of other lymphomas may experience immune dysregulation similar to survivors of DLBCL. Comparing survivors of DLBCL to survivors of Hodgkin lymphoma (HL), another hematologic malignancy with significant disease-free, treatment-free survival, we found 10 diagnoses differentially incident. All but one was more common among survivors of DLBCL, and 3 met the adjusted significance threshold of $P \leq .0002$ (Data Supplement), suggesting less difference in immune health between survivors of DLBCL and HL than in the other comparisons.

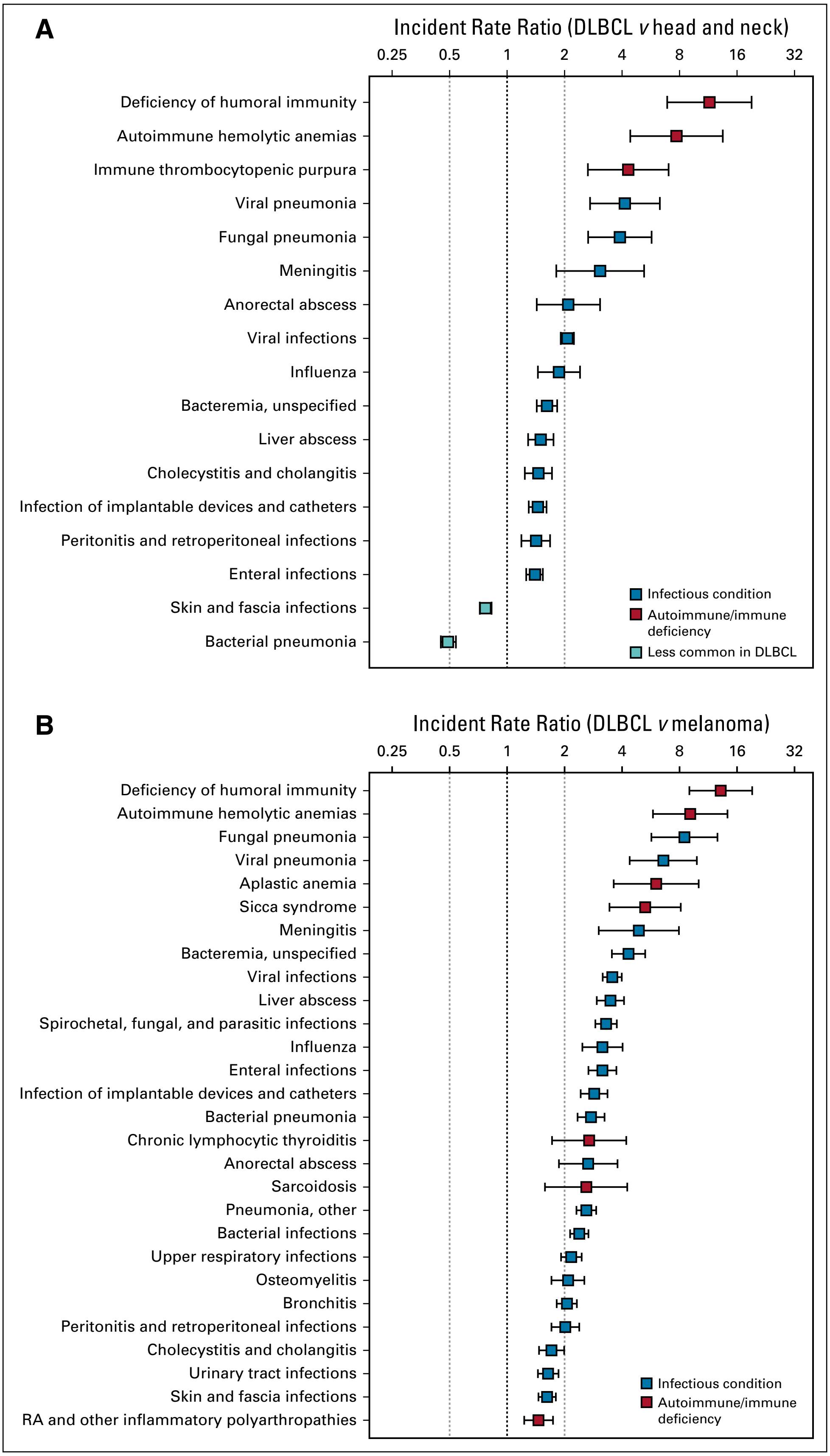

FIG 2. Estimated incidence rate ratios of autoimmune, immune deficiency, and infectious conditions among survivors of B-cell lymphoma (DLBCL) compared with survivors of (A) head and neck cancer and (B) melanoma in the 1-10 years after cancer diagnosis, California, 1991-2012. Models were adjusted for age, race, sex, and year of cancer diagnosis. Error bars show 95% CIs. Only diagnoses for which the comparison yielded a *P* value ≤ .0002 are shown. Log2 scale is used for the *x*-axis. RA, rheumatoid arthritis.

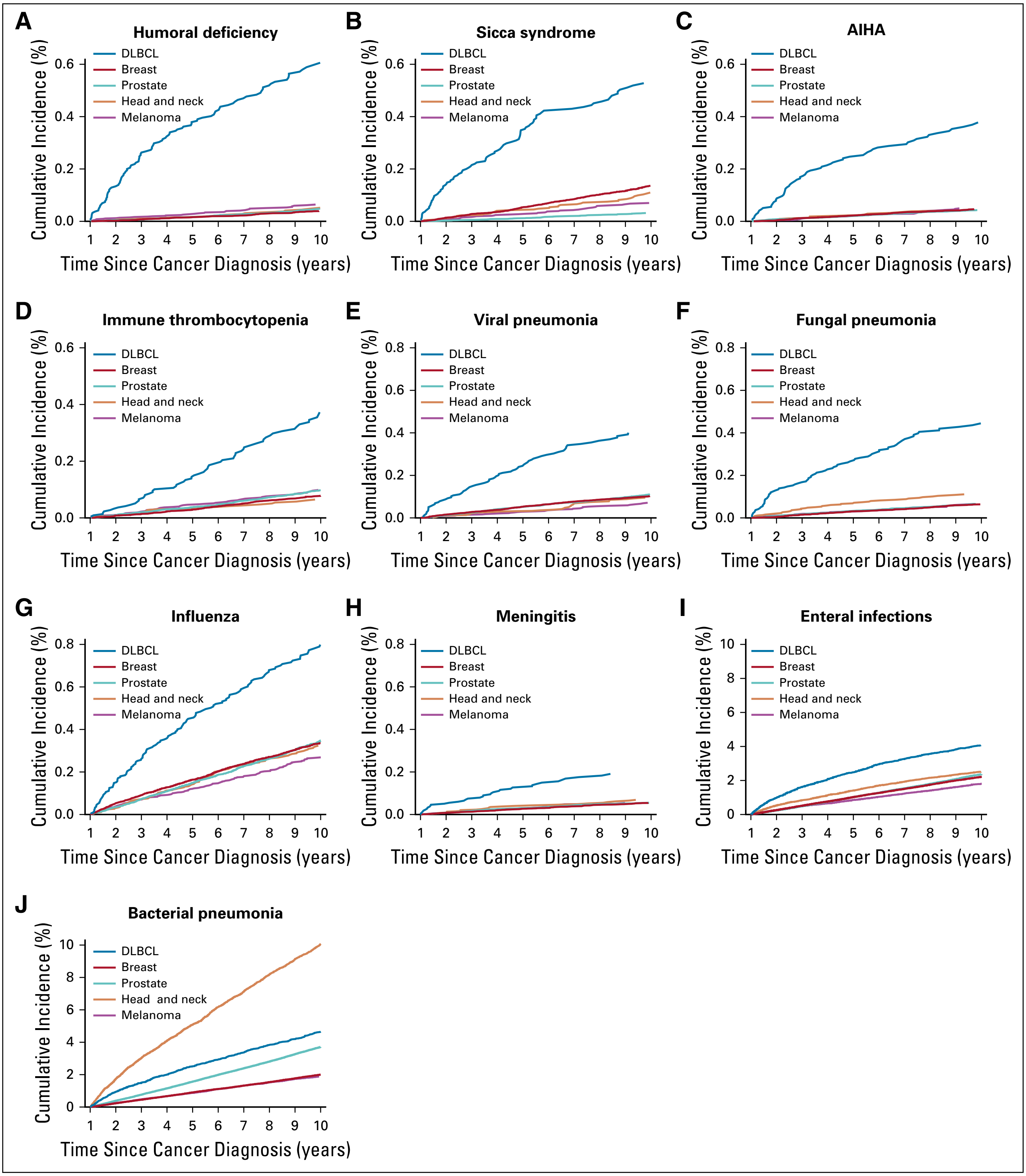

FIG 3. Cumulative incidence curves for (A) humoral deficiency, (B) sicca syndrome, (C) autoimmune hemolytic anemia (AIHA), (D) immune thrombocytopenia, (E) viral pneumonia, (F) fungal pneumonia, (G) influenza, (H) meningitis, (I) enteral infections, and (J) bacterial pneumonia for each cohort of cancer survivors as indicated in the graph legends, from 1-10 years after initial cancer diagnosis. DLBCL, diffuse large B-cell lymphoma.

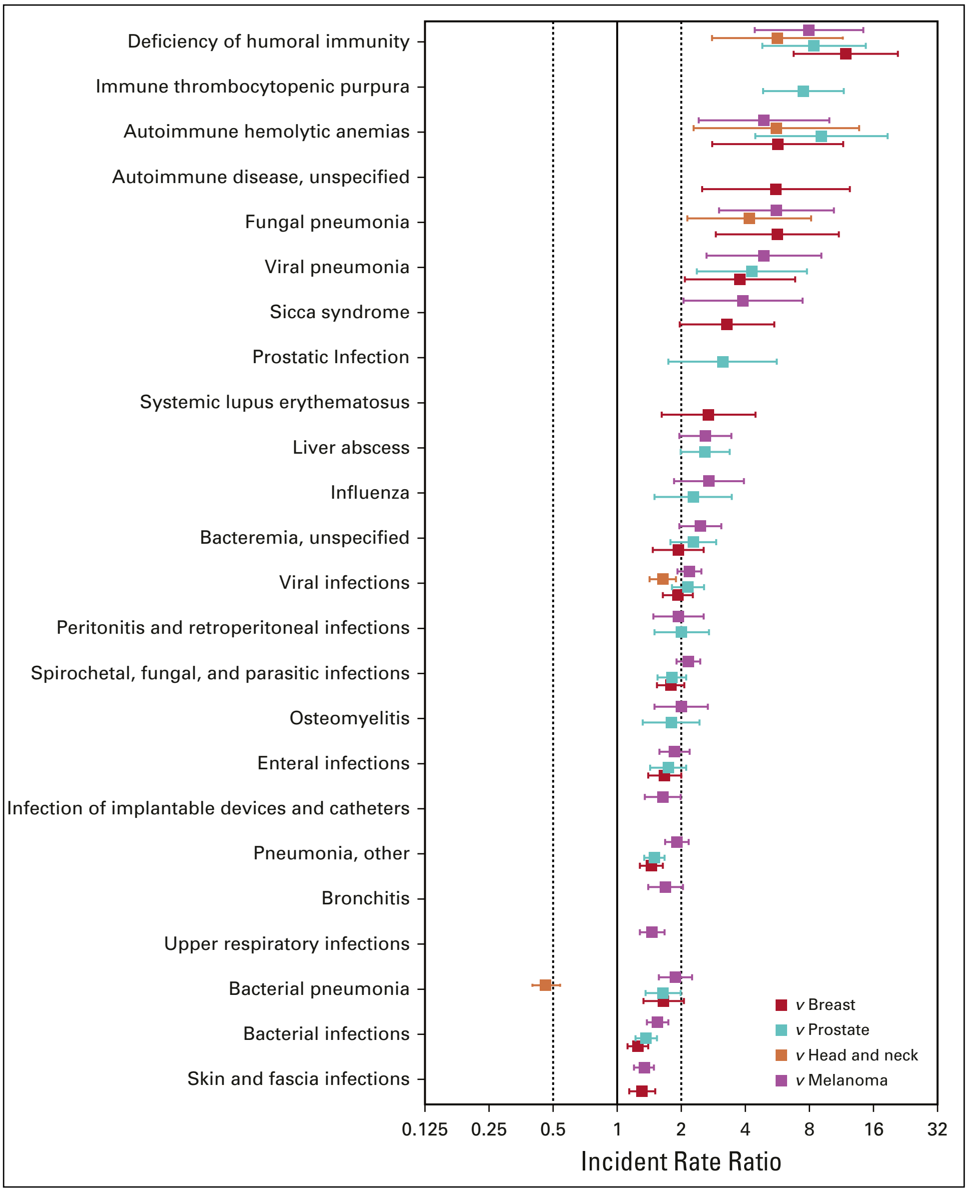

FIG 4. Estimated incidence rate ratios (IRRs) among survivors of diffuse large B-cell lymphoma compared with each of the four comparison cohorts during years 5-10 after cancer diagnosis. Error bars show 95% CIs. Only diagnoses for which the IRR had a *P* value ≤ .0002 are shown. Log2 scale is used for the *x*-axis.

Full Landscape of Immune-Related Excess Risks Among Survivors of DLBCL

For a broader assessment of immune dysregulation in survivors of DLBCL we performed a secondary analysis that captured all 595 immune-related diagnosis codes, categorized into 18 clinical groupings (Data Supplement). Survivors of DLBCL had higher incidence of specific immune deficiencies (IRRs, 7.0-13.3); hematologic autoimmune conditions (IRRs, 1.9-3.1); gastrointestinal, renal, and hepatic conditions (IRRs, 1.4-2.3); and diffuse autoimmune diseases (IRRs, 1.2-1.6) across all 4 comparisons and other categories across 2-3 comparisons (Fig 5; Data Supplement). Survivors of head and neck cancer experienced more skin and bone infections (IRR, 0.76; 95% CI, 0.70 to 0.82), respiratory infections (IRR, 0.86; 95% CI, 0.81 to 0.91), and oral infections (IRR, 0.10; 95% CI, 0.06 to 0.17).

DISCUSSION

In survivors of DLBCL compared with survivors of four different cancers, we demonstrate significantly increased incidence of infectious conditions, immune deficiencies, and autoimmune diseases, notably viral and fungal pneumonias, meningitis, humoral deficiency, hematologic autoimmune conditions, and sicca syndrome. Through multiple sensitivity analyses, we show that the majority of these excess risks are not driven by exposure to systemic chemotherapy, SCTs, or rituximab. We also show that excess risks are not driven by relapsing disease, as they persist during disease-free, treatment-free, long-term

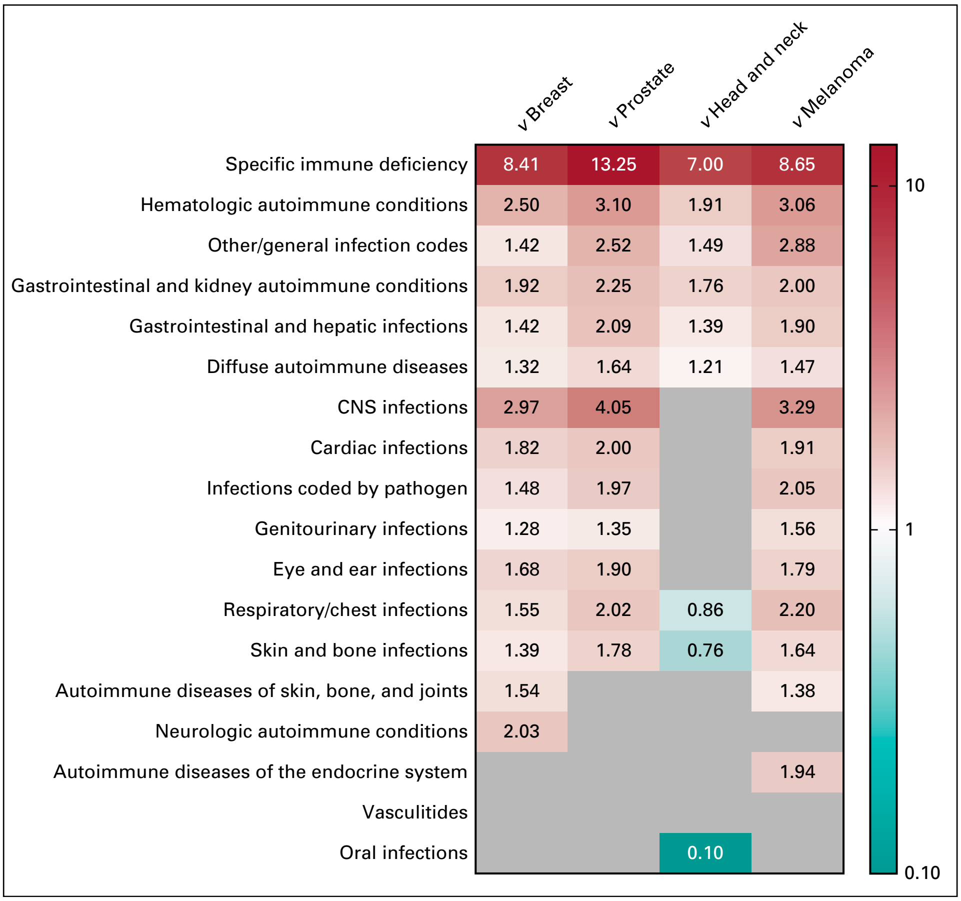

FIG 5. Incident rate ratios for 18 categories of immune-related conditions (autoimmune diseases, immune deficiencies, and infectious diseases) among survivors of diffuse large B-cell lymphoma (DLBCL) compared with survivors of breast cancer, prostate cancer, head and neck cancer, or melanoma. Results reaching a *P* value ≤ .0002 are shown, and the remainder are grayed. Color scale is logarithmic ($\log^{10}$), with pink and red shading for categories of diagnoses found more commonly in survivors of DLBCL and green shading for categories of diagnoses found more commonly in the comparator cohort.

survival, determined by studying 5-year survivors and by exclusion of patients with relapsed/refractory disease.

It is intriguing that diagnoses commonly concurrent with lymphoma, such as autoimmune hemolytic anemia, immune thrombocytopenia, and sicca syndrome, were also likely to arise during DLBCL survivorship. It is unlikely that these conditions simply failed to be excluded as preexisting conditions, because similar results were seen in the analysis of late survivorship, where conditions recorded up to 5 years after cancer diagnosis were excluded. These autoimmune conditions may develop because of long-lasting changes to immune networks by lymphoma and/or past treatments. Alternatively, they may exist subclinically, be resistant to lymphoma treatments, and manifest later in life. Evidence from preclinical models suggests clonal relationships between self-reactive and malignant B-cell clones can exist,[39] which may also explain why known lymphoma-related conditions emerged with the strongest signals.

Humoral deficiency (ie, hypogammaglobulinemia) was much more common in survivors of DLBCL. Approximately 15% of patients with DLBCL have hypogammaglobulinemia at diagnosis, and another 40% develop it after treatment with rituximab.[40] Delayed or persistent hypogammaglobulinemia has been observed in rituximab-treated patients.[41-43] We observed substantially higher IRRs for humoral deficiency after the introduction of rituximab than in the years prior. Interestingly, no other diagnosis was consistently different across cohorts after the introduction of rituximab, suggesting that most of the excess risks we observed cannot be attributed to rituximab exposure.

Survivors of DLBCL experienced increased incidence of many infections, particularly viral and fungal infections, the immune response to which relies on innate immune cells and T cells, signaling the breadth of immune dysfunction seen in survivors of a B-cell lymphoma. These risks were similar when we controlled for the effects of systemic chemotherapy, SCTs, or rituximab, suggesting they may be driven by lymphoma biology or by unevaluated factors. Although we did not directly assess the impact of infections on mortality, increased mortality from infections has been demonstrated for survivors of DLBCL, including those who survived ≥ 5 years.[44]

The few immune-related diagnoses more frequent in the comparator cohorts were known or plausible associations. Survivors of head and neck cancer are at high risk for skin, oral, and lung infections as a result of impairments wrought by cancer, surgery, radiation, and chemotherapy,[45,46] and these higher risks were evident in our study. Increased incidence of cervicitis among survivors of breast cancer has not previously been demonstrated, but low estrogen states confer greater susceptibility to cervicitis,[47] and many patients with breast cancer are induced into low-estrogen states as part of their treatment.

This study was strengthened by the use of a large, complete, population-based cohort of patients with cancer and its linkage to a comprehensive, statewide database of hospitalizations, emergency room visits, and ambulatory surgery visits. By comparing survivors of DLBCL to survivors of several other cancer types, we were able to uncover differences likely to be specific to lymphoma. The consistency of our results across cancer cohorts strengthens the findings, and by excluding conditions occurring up to 1 year after cancer diagnosis (or up to 5 years in a secondary analysis), we were able to focus on conditions with presumed onset during survivorship.

There are limitations to our study. We captured noncancer diagnoses only for cancer survivors who visited a hospital or emergency department or had ambulatory surgery. Without data from outpatient clinic visits, our results likely underestimate the absolute incidence of these conditions. This limitation applies to each survivor cohort; therefore, IRRs should be accurate measures of relative incidence. The data sources may introduce ascertainment bias toward diagnoses more likely to result in hospital, emergency room, or ambulatory surgery encounters, although this may also impart greater clinical significance, because of the associated morbidity and health care utilization.

The study findings are also limited by differences in disease biology and treatment across cohorts; however, comparison of DLBCL to several disparate cancers mitigates this concern, and the consistency across comparisons and sensitivity analyses controlling for major treatment differences strengthens our findings. DLBCL was our chosen model for hematologic malignancy because of sufficient prevalence and extended disease-free survival. We attempted to determine whether immune dysregulation may plague survivors of other hematologic malignancies via a limited comparison with HL. Many fewer conditions were differentially incident in this analysis relative to the comparisons against solid tumors, suggesting that factors intrinsic to the etiology of lymphoid malignancy may contribute to impaired immune health during survivorship.

Our findings support the hypothesis that immune derangements in survivors of DLBCL can be both wide ranging and long lasting. A better understanding of the increased health risks and resultant morbidity and mortality faced by survivors of lymphomas is now needed to identify opportunities to intervene. These data should also motivate longer-term follow-up of patients with DLBCL in interventional trials to capture differences in these late effects and to detect risks that may be associated with newer therapies.

Except for after SCT, there are no specific guidelines for vaccination of survivors of DLBCL, yet we observed higher rates for vaccine-preventable diseases such as influenza and bacterial pneumonias, suggesting a potential role for standardized vaccination of all patients with DLBCL. For current clinical practice, efforts to follow existing general vaccination recommendations should be redoubled, as vaccination rates among patients with DLBCL[48] are poor.

To our knowledge, this is the first study to show significant and widespread increases in the risks for infectious conditions, immune deficiencies, and autoimmune diseases among survivors of DLBCL. Understanding the underlying biology of these excess immune risks will help improve the care of survivors of DLBCL and may ultimately direct improvements in the clinical management of lymphoma.

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01937.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impaired Immune Health in Survivors of Diffuse Large B-Cell Lymphoma

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